Secondary Hematologic Malignancies in Patients Following CD19 CAR T-Cell Therapy: Aggregated Clinical Trial Data from 1542 Patients

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INTRODUCTION

CAR T-cell Therapy: An Effective Treatment

- Over 30,000 patients with leukemia, lymphoma and myeloma have received CAR T-cell therapy
- Autologous T-cells are genetically modified to target tumors and then reinfused into patients after lymphodepleting chemotherapy

Recent US FDA Alert:

- The FDA is investigating 22 patients who developed T-cell lymphoma after receiving CAR T-cell therapy (targeting CD19 or BCMA)[1].
- Boxed warnings have been added to all approved CAR T-cell therapies regarding secondary myeloid malignancies and T-cell lymphomas.

Increased Risk of Secondary Malignancies:

- Patients treated for hematologic malignancies face higher risks of secondary cancers, in part due to previous chemotherapy exposure.
- Although patients can clearly develop second cancers after CAR T-cell therapy, whether / to what extent the CAR T-cells themselves contribute to this risk is unknown

AIM

Quantify the incidence of second primary malignancies in a large cohort of patients who have received CAR T-cells while enrolled in clinical trials.

These data offer the high quality, granularity and accuracy of clinical trial data but the aggregation offers a larger denominator of patient-years in which to evaluate incidence.

METHODS

Data Source and Patient Identification

- All patients with lymphoma who were treated with CD19-directed CAR T-cells in clinical trials were identified from the Medidata Clinical Cloud®, which houses aggregated, anonymized trial data.

Incidence of Second Primary Malignancies

- The occurrence of second primary hematologic malignancies was calculated, excluding second B-cell lymphomas given that these likely represent relapse of the primary disease.

Survival Analysis

- Overall survival (OS) and progression-free survival (PFS) were assessed using the Kaplan-Meier method.

ACKNOWLEDGEMENTS

We would like to acknowledge the clinical trial participants.

RESULTS

Table 1. Patient Demographics

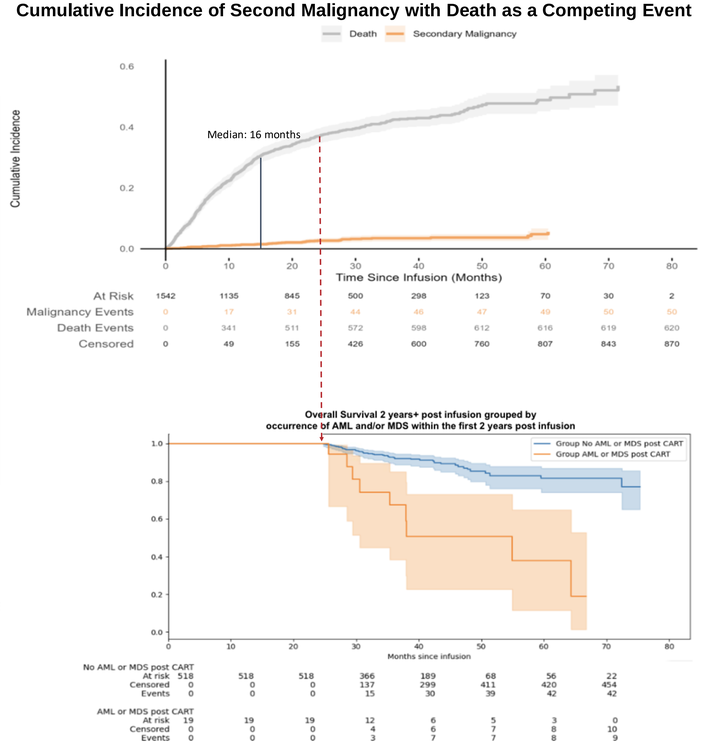
	Number of patients
Total Number of patients treated with CD19-directed CAR T-cells	1542
Median Follow-up	24 months (3133 patient-years)
Median Age	61 years
Types of Lymphoma	• Diffuse large B-cell lymphoma (63%) • Mantle cell lymphoma (12%) • Follicular lymphoma (17%)
Median prior lines of treatment (excluding bridging therapy)	2
Second Hematologic Malignancies	53 patients: • AML: 14 patients • MDS: 40 patients (4 had both AML and MDS) • Multiple Myeloma: 2 patients • Peripheral T-cell lymphoma: 1 patient

Case Highlight:

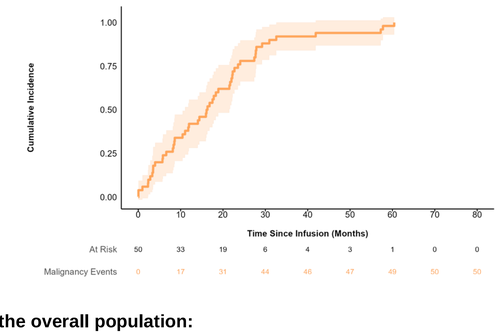
- One patient developed T-cell lymphoma after CAR T-cell therapy, following 3 prior treatment lines including autologous stem cell transplantation.
- The patient passed away 1 month after the diagnosis. Whether the lymphoma conta the CAR construct was not known from this database.

Key Data: Overall second hematologic malignancy incidence: 2.45% per patient-year.

Cumulative Incidence of Second Malignancy with Death as a Competing Event



Cumulative Incidence of Second Malignancy over time (Among patients who develop Second Malignancy [N=50])



In the overall population:

- The incidence of second malignancies is ~2.5% per year following CAR T treatment in the first 2 years
- The overall non-time adjusted incidence of second hematologic malignancies is ~3.24%.
- Unsurprisingly, for patients who do develop second malignancies, their survival rates are significantly worse from the time of onset of those second malignancies than those patients who survive through the initial 2 years post CAR-T (the time of highest risk for relapse) who do not develop secondary malignancies

In patients with AML and/or MDS

- The cumulative incidence of second malignancies rises sharply during the first 20 months (median onset 16 months). This early peak raises questions regarding the causes and predictability of these malignancies.
- Longer follow-up is required to determine whether this risk plateaus over time or continues to increase

CONCLUSIONS

Observed Rates of Second hematologic malignancy:

- Second hematologic malignancy rate: 2.45% per patient-year.
- Comparable to previous data on lymphoma patients treated with other cellular therapies like autologous or allogeneic stem cell transplants (SCT).

Comparison with existing literature:

- T-cell malignancy was exceedingly rare, reported in only a single patient (<0.01%).
- These data corroborate a recent meta-analysis which evaluated 7604 patients for causes of non-relapse mortality (Dos Santos et al., Nat Med 2024), finding zero deaths secondary to T-cell lymphoma.

Clinical Perspective:

CAR T-cells remain a valuable treatment for patients with lymphoma, and both clinicians and patients should carefully weigh the risks of secondary malignancies in the context of overall treatment benefits.

Vigilance and Context:

- For patients whose primary malignancy is effectively treated by CAR T and who are long-lived after treatment, surveillance for secondary malignancies – especially myeloid cancers – is warranted as these secondary cancers represent a significant risk of death for these patients over the lifespan.
- Need for vigilance regarding CAR-mediated insertional mutagenesis and T-cell lymphoma risk, although with reassurance to patients that this remains very rare
- Important to further investigate reported cases to determine how many contained the CAR construct.
- Clinical trial records must be bolstered by real world evidence to provide the most accurate overall picture regarding treatment toxicity

Open Questions:

It remains unclear to what extent CAR T-cells propagate clonal expansion (CHiP) and/or how CAR-T induced immunosuppression contributes to malignancy risk. The degree of contribution of bridging therapy remains unknown.

REFERENCES

1. US Food and Drug Administration. FDA Investigating Serious Risk of T-cell Malignancy Following BCMA-Directed or CD19-Directed Autologous Chimeric Antigen Receptor (CAR) T cell Immunotherapies. November 28, 2023 (https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/fda-investigating-serious-risk-t-cell-malignancy-following-bcma-directed-or-cd19-directed-autologous)
2. Cordas Dos Santos DM, Tix T, Shouval R, et al. A systematic review and meta-analysis of nonrelapse mortality after CAR T cell therapy. Nature Medicine. 2024;30(9):2667-2678. doi:10.1038/s41591-024-03084-6

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